SYNTHESIS

Zapping Diels-Alder reactions

Electric field spurs reagents to join up in nonredox transformation

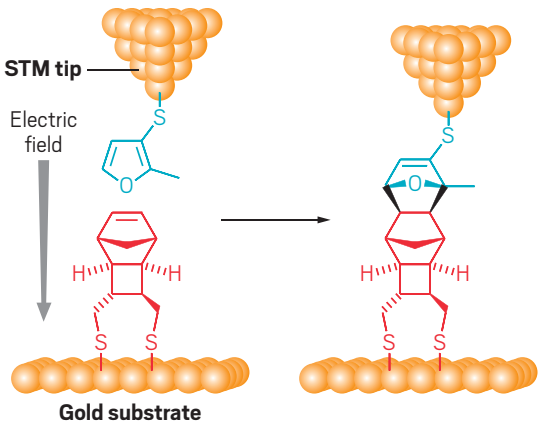
In a discovery that might come as a shock—or, at the very least, an electric shock—chemists have found that a properly oriented external electric field can nudge two reagents to hook up with one another in a Diels-Alder reaction. The fundamental discovery expands chemists' knowledge of how electricity can drive synthesis and catalysis (*Nature* 2016, DOI: 10.1038/nature16989).

Chemists have long used electricity to trigger redox reactions. And theorists have suggested that electric fields could spur on nonredox transformations, but until now, no one had shown this was possible with a bimolecular system. "What is particularly striking is that we chose a really simple nonpolar carbon-carbon bond-forming reaction—a Diels-Alder reaction—for which there are no formal zwitterionic intermediates involved," says Michelle L. Coote, a professor at Australian National University who coauthored the study. "So we think these electric field effects could be very general."

Coote and her collaborators were inspired by the work of Hebrew University of Jerusalem theorist Sason Shaik, who suggested that an oriented electric field might accelerate Diels-Alder reactions. To prove this experimentally, Coote and her colleagues tethered a dienophile to a gold surface and a diene to the tip of a scanning tunneling microscope.

They brought the molecules close to one another and applied an electric field. Upping the power of the electric field led to an increase in the reaction rate. What's more, the field's polarity mattered: The reaction rate only got a boost when the electric field favored electron flow from the dienophile to the diene.

Shaik tells C&EN he was delighted to see his theory, which had been described as "daydreaming," proven experimentally.



Shocking **An electric field can trigger a Diels-Alder reaction.**

Although the current method can't synthesize products on a practical scale, he thinks the discovery has the potential to change how chemists make molecules. "I definitely see a future where instead of mixing chemicals in a flask and heating, you will zap molecules with an electric field," he says.—BETHANY HALFORD

NEUROSCIENCE

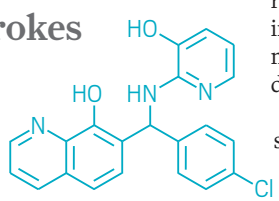
Preventing damage from brain bleeds

Strategy may protect brain function after some strokes

Although the number of people dying from stroke has been dropping, it is a leading cause of disability in adults in the U.S.

An international team of researchers now reports a possible strategy to prevent the long-term neurological damage that occurs after strokes involving intracerebral hemorrhage, or bleeding in the brain. They show that inhibiting a metalloenzyme in neurons improves neurological function in rodents experiencing brain hemorrhages (*Sci. Transl. Med.* 2016, DOI: 10.1126/scitranslmed.aac6008).

Neurologists studying intracerebral hemorrhage have found that as blood cells spill into surrounding brain tissue, they rupture and release their molecular contents, including iron-containing proteins, which can directly or indirectly injure neurons. In animal studies, iron chelators have mitigated some of this damage.



Adaptaquin

These molecules do so not by sequestering spilled iron, which can produce destructive oxygen radicals, but by inhibiting iron-containing enzymes. These enzymes add hydroxyl groups to gene-regulating proteins called transcription factors to control their function.

But iron chelators aren't ideal therapeutics: They could interfere with normal iron-mediated processes in cells, causing unwanted side effects. So, in a previous study, Rajiv R. Ratan, executive director of Burke Medical Research Institute, and colleagues screened 85,000 small molecules to find specific inhibitors of the metalloenzymes.

For the new work, they tested the best inhibitor, a branched hydroxyquinoline they call adaptaquin, in two rodent models of intracerebral hemorrhage. Mice and rats receiving adaptaquin nearly recovered normal neurological function in tests of behaviors typically impaired by stroke, such as motor skills and spatial awareness.

Michael Tymianski, a neurosurgeon at the University of Toronto, says the researchers not only provide compelling evidence that they could improve outcomes after hemorrhage, but also describe a plausible mechanism underlying adaptaquin's action. Also, by testing the inhibitor in two rodent models, it is more likely that the results could be translated to people in the clinic. "This study is not only novel," he says, "but also head and shoulders above other studies typically published in the area of intracerebral hemorrhage research."—MICHAEL TORRICE

ADAPTED FROM *NATURE*